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(54) Title: ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract

Novel indane and indene derivatives are described which are endothelin receptor antagonists.

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ENDOTHELIN RECEPTOR ANTAGONISTS

FIELD OF INVENTION

The present invention relates to novel indane and indene derivatives, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists.

BACKGROUND

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. Of these, only ET-1 and ET-3 have been found to be expressed in mammalian systems. [Unless otherwise stated "endothelin" shall mean any or all of the isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of endothelin have been reported in plasma from patients with essential hypertension, acute

myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia und rgoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

Endothelin appears to produce a preferential effect in the renal vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity and chronic renal failure.

Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and often fatal consequence of subarachnoid hemorrhage.

ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

ET has also been implicated in myocardial ischemia (Nichols et al. Br. J. Pharm. 99: 597-601, 1989 and Cloz 1 and Clozel, Circ. Res., 65: 1193-1200, 1989)

coronary vasospasm (Fukuda et al., Eur. J. Pharm. 165: 301-304, 1989 and Lüscher, Circ. 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, Biochem & Biophys. Res. Commun.; 168: 537-543, 1990, Bobek et al., Am. J. Physiol. 258:408-C415, 1990) and atherosclerosis, (Nakaki et al., Biochem. & Biophys. Res. Commun. 158: 880-881, 1989, and Lerman et al., New Eng. J. of Med. 325: 997-1001, 1991). Increased levels of endothelin have been shown after coronary balloon angioplasty (Kadel et al., No. 2491 Circ. 82: 627, 1990).

Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including human bronchus (Uchida et al., Eur J. of Pharm. 154: 227-228 1988, LaGente, Clin. Exp. Allergy 20: 343-348, 1990; and Springall et al., Lancet, 337: 697-701, 1991).

Endothelin has been associated with the induction of haemorrhagic and necrotic damage in the gastric mucosa (Whittle et al., Br. J. Pharm. 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello et al., Lancet 337: 114-115, 1991); Migraine (Edmeads, Headache, Feb. 1991 p 127); Sepsis (Weitzberg et al., Circ. Shock 33: 222-227, 1991; Pittet et al., Ann. Surg. 213: 262-264, 1991), Cyclosporin-induced renal failure or hypertension (Eur. J. Pharmacol., 180: 191-192, 1990, Kidney Int, 37: 1487-1491, 1990) and endotoxin shock and other endotoxin induced diseases (Biochem. Biophys. Res. Commun., 161: 1220-1227, 1989, Acta Physiol. Scand. 137: 317-318, 1989).

Thus, endothelin receptor antagonists would offer a unique approach toward the pharmacotherapy of hypertension, renal failure, cerebrovascular disease, myocardial ischemia, angina, heart failure, asthma, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma, endotoxin shock, endotoxin induced

multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty and prevention of restenosis.

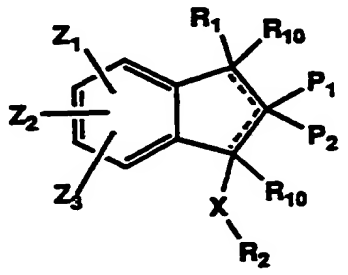
SUMMARY OF THE INVENTION

This invention comprises indane and indene derivatives represented by Formula (I) and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the treatment of a variety of cardiovascular and renal diseases including but not limited to: hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, stroke, cerebrovascular vasospasm, myocardial ischemia, angina, heart failure and atherosclerosis.

This invention further constitutes a method for antagonizing endothelin receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

DETAILED DESCRIPTION OF THE INVENTION

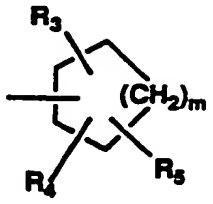
The compounds of this invention are represented by structural Formula (I):



(I)

wher in:

R_1 is $-X(CH_2)_nAr$ or $-X(CH_2)_nR_8$ or



(c) ;

R_2 is hydrogen, Ar or (c);

P_1 is $-X(CH_2)_nR_8$;

P_2 is $-X(CH_2)_nR_8$, or $-XR_9Y$;

R_3 and R_5 are independently hydrogen, R_{11}, OH, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl, CF_3, $NHCOR_6$, $-R_{11}CO_2R_7$, $-XR_9-Y$ or $-X(CH_2)_nR_8$ wherein the methylene groups of $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or more $-(CH_2)_nAr$ groups;

R_4 is hydrogen, R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, $-X(R_{11})$, Br, F, I, Cl or $NHCOR_6$ wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-4}alkyl;

R_7 is independently hydrogen, C_{1-6}alkyl or $(CH_2)_nAr$;

R_8 is hydrogen, R_{11}, CO_2R_7, PO_3H_2, $P(O)(OH)R_7$, CN, $-C(O)N(R_6)_2$, tetrazole or OR_6;

R_9 is C_{1-10}alkyl, C_{2-10}alkenyl or phenyl all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, COOH, halogen or XC_{1-5}alkyl;

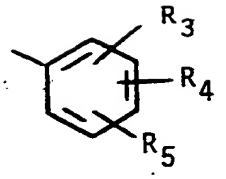
R_{10} is R_3 or R_4;

R_{11} is C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

X is $(CH_2)_n$, O, NR_6 or $S(O)_q$;

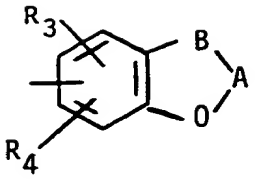
Y is CH_3 or $X(CH_2)_nAr$;

Ar is:



(a)

or



(b)

or

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, oxazolyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more R_3 or R_4 groups;

A is C=O, or $[C(R_6)_2]_m$;

B is $-CH_2-$ or $-O-$;

Z_1 and Z_2 are independently hydrogen, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, OH, C_{1-8}alkoxy, $S(O)_qC_{1-8}$alkyl, $N(R_6)_2$, Br, F, I, Cl, $NHCOR_6$, $-X(CH_2)_nR_8$, phenyl, benzyl or C_{3-6}cycloalkyl wherein the C_{1-8}alkyl, C_{2-8}alkenyl or C_{2-8}alkynyl may be optionally substituted by COOH, OH, $CO(CH_2)_nCH_3$, $CO(CH_2)_nCH_2N(R_6)_2$, or halogen; or Z_1 and Z_2 together may be -O-A-O- on contiguous carbons;

Z_3 is Z_1 or XR_9Y;

q is zero, one or two;

n is an integer from 0 to six;

m is 1, 2 or 3;

and the dotted line indicates the optional presence of a double bond; or a pharmaceutically acceptable salt thereof; provided that

- R_2 is not hydrogen when X is $S(O)_q$;
- when the optional double bond is present there is only one R_{10} and there is no P_1;
- the compound of Formula I is not (1RS)-1,3-diphenylindene-2-carboxylic acid; (cis,cis)-

(1RS,3SR)-1,3-diphenylindane-2-carboxylic acid; (1RS)-3-[3-Methyl-1-phenyl-(1H)-ind-2-en-1-yl] propionic acid; or (1RS)-2[1,3-diphenyl-(1H)-ind-2-en-2-yl]ethanoic acid.

Also included in the invention are pharmaceutically acceptable salt complexes.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. The term "halogen" is used to mean iodo, fluoro, chloro or bromo. Alkyl groups may be substituted by one or more halogens up to perhalogenation.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and diastereoisomers are contemplated to be within the scope of the present invention.

Preferred compounds are those wherein R_1 is $X(CH_2)_nAr$, (Ar is (a) or (b)), dihydrobenzofuranyl, benzodioxanyl, cyclohexyl, C_{1-4}alkyl; R_2 is (a), (b) C_{1-4}alkyl, indolyl or hydrogen; R_3 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, halogen, $-OC_{1-4}$alkyl phenyl, $R_{11}CO_2R_7$, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$, $-X(CH_2)_nR_8$, $-XR_9$ pyridyl, phenyl or $S(O)_pC_{1-5}$alkyl; R_4 is hydrogen, OH, C_{1-5}alkoxy, halogen, C_{1-4}alkyl, $N(R_6)_2$, $NH(CO)CH_3$ or $S(O)_pC_{1-5}$alkyl; Z_1, Z_2 and Z_3 are independently XR_9Y, benzyl, hydrogen, OH, C_{1-5}alkoxy, $-N(R_6)_2$, $S(O)qC_{1-8}$alkyl, $NHCOR_6$, $X(CH_2)_nR_8$ or halogen, or Z_1 and Z_2 together may be -O-A-O on contiguous carbons; P_1 and P_2 are independently hydrogen, CO_2H or tetrazole; Ar is (a), (b), phenyl, or pyridyl; X is $(CH_2)_n$ or oxygen.

More preferred are compounds wherein R_3 is hydrogen or $-X(CH_2)_nR_8$, $R_{11}CO_2R_7$; R_4 and R_5 are independently hydrogen, OH, C_{1-5}alkoxy, SC_{1-5}alkyl, F, Br, C_{1-3}alkyl or NH_2; Z_1 and Z_3 are hydrogen and Z_2 is hydrogen, OH, C_{1-5}alkoxy, halogen, $X(CH_2)_nR_8$, NH_2, benzyl, $NH(CO)CH_3$, or Z_1 and Z_2 together may be O-A-O.

Most preferred are compounds wherein R_1 is (b) and R_2 is (a) r (b); A is CH_2, B is -O-; there is no optional double bond; R_1 and XR_2 are trans to P_1; Z_2 is OH, C_{1-5}alkoxy, $-OCH_2CHCH_2$ or hydrogen, Z_1 is hydrogen; R_3 is hydrogen, $X(CH_2)_qCOOH$ or $CH=CHCO_2H$, R_4 is hydrogen, substituted phenyl, or C_{1-2}alkoxy; and R_5, R_{10} and P_2 are hydrogen.

Especially preferred are the following compounds:

(1RS, 2SR, 3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid;

(1RS, 2RS, 3SR)-5-Hydroxy-3-(4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid;

(1RS, 2RS, 3SR)-5-Methoxy-3-(4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid;

(1RS, 2SR, 3SR)-1,3-Bis(3,4-methylenedioxyphenyl)-5-5-hydroxyindane-2-carboxylic acid;

(1RS,2SR,3RS)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid

(1RS, 2SR, 3SR)-3-(2-Carboxymethoxy-4-methoxyphenyl)-1-(2-methoxy-4,5-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid

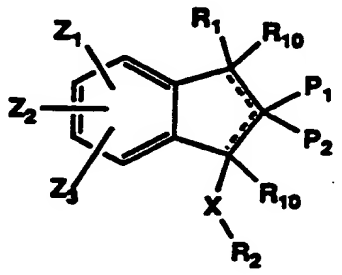
(1RS, 2SR, 3RS)-3-[2-(1-Carboxyeth-2-yloxy)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid, bis-dicyclohexylamine salt;

(1RS, 2SR, 3SR)-3-[2-[(E)-2-Carboxyethen-1-yl]-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid;

(1RS, 2SR, 3SR)-3-[2-(2-Carboxyeth-1-yl)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid;

(1RS,2SR,3RS)-3-[2-(3-Carboxyphenyl)-4-methoxyphenyl]-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)indane-2-carboxylic acid

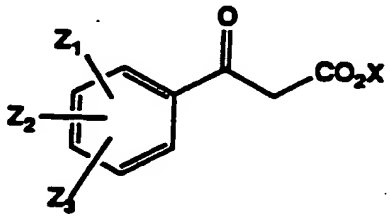
The present invention provides compounds of Formula (I) above



(I)

which can be prepared by a process which comprises:

a) reacting a compound of Formula (2) wherein X is C_{1-5}alkyl

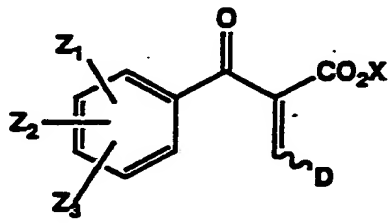


(2)

with a substituted benzaldehyde or aldehyde of Formula (3).

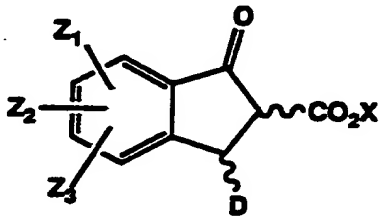
D-CHO (3)

wherein D is Ar or (c) as defined in Formula I, in a suitable solvent such as benzene with a catalyst such as piperidinium acetate at reflux to provide a compound of Formula (4).



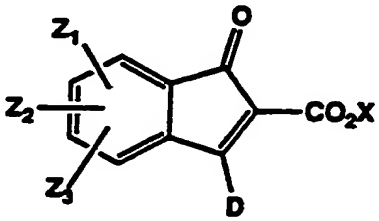
(4)

Cyclization of compound (4) in the presence of a suitable Lewis acid such as titanium tetracholoride or aluminum chloride or alternatively when Z_1 is 3-OR (meta) (where R is C_{1-5}alkyl, or benzyl), trifluoroacetic acid, provides an indanone of the Formula (5).



(5)

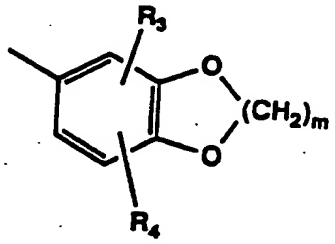
Dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in an appropriate solvent or alternatively bromination with pyridinium hydrobromide perbromide in dichloromethane followed by treatment with 1,5-diazabicyclo[4,3,0]non-5-ene provides indenones of Formula (6).



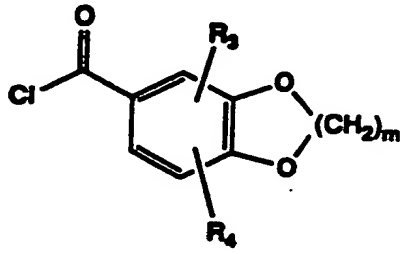
(6)

b) Alternatively, a compound of Formula 6 wherein Z_1, Z_2 and Z_3 are hydrogen and

D =

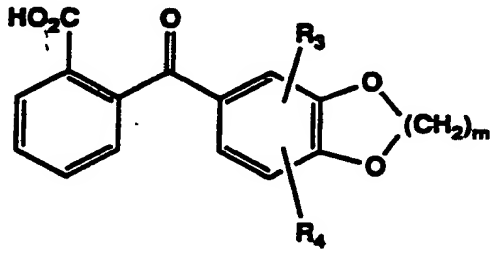


can be prepared by treatment of 2-bromobenzoic acid with two equivalents of n-butyllithium in a solvent such as tetrahydrofuran under argon at -78 C followed by the addition of an acid chloride of formula (7):



(7)

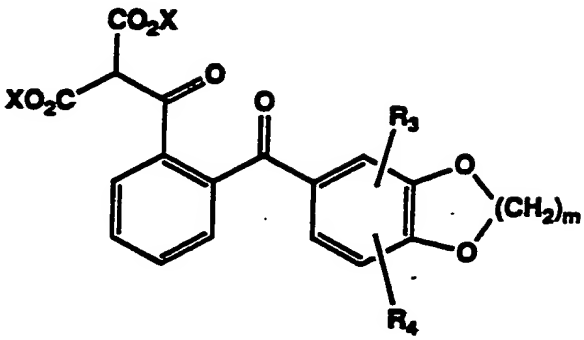
provides a compound of formula (8):



(8)

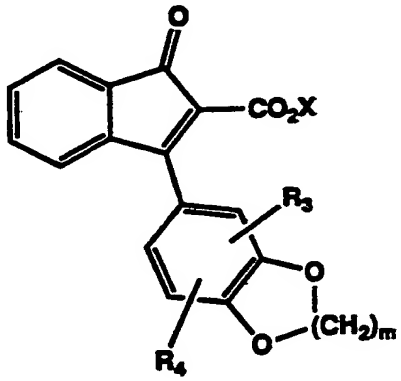
Treatment of compounds of type (8) with thionyl chloride at reflux gives an acid chloride which can be isolated by concentration under reduced pressure. This acid chloride can then be treated with diethyl

magnesium mal nate in a solvent such as ether to give a compound of formula (9):



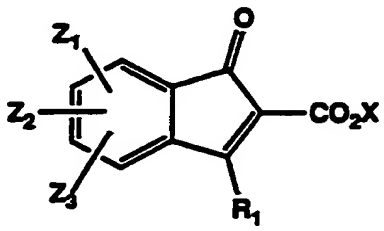
(9)

Reaction of a compound of type (9) at reflux with 5% aqueous sodium carbonate gives compounds of formula (10):



(10)

c) Treatment of an indenone of formula (11):

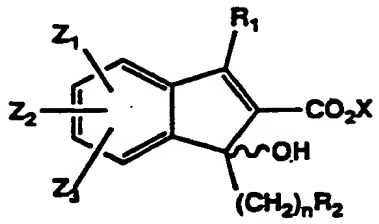


(11)

wherein Z_1, Z_2, Z_3 and R_1 are as defined for formula I or a group convertable to them, with an organomagnesium compound of Formula (12) wherein R_2 is defined for

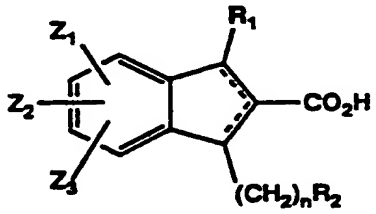
$$R_2(CH_2)_nMgBr \qquad (12)$$

Formula I or a group convertabl to it, in a suitable solvent at 0°C provides compounds of formula (13):



(13)

Saponification of compounds of formula (13) using sodium hydroxide in aqueous methanol followed by reduction with triethylsilane and boron trifluoride etherate in a suitable solvent such as dichloromethane at 0°C affords racemic compounds of formula (14).

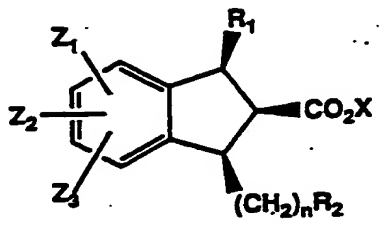


(14)

Conjugate addition of nucleophiles to an ester derived from formula (14), followed by saponification affords compounds of formula (I) having an R_{10} other than hydrogen. Re-introduction of a double bond into an ester derived from such acids followed by conjugate addition of another nucleophilic species and subsequent saponification affords compounds of formula (1) in which neither R_{10} substituent is hydrogen.

Reduction of compounds of formula (13) with triethylsilane and boron trifuoride etherate in a suitable solvent such as dichloromethane at 0°C followed by hydrog nation with hydrogen gas under pressure at

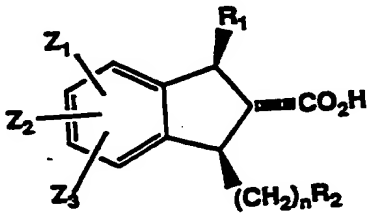
approximately 60 psi in the presence of a suitable catalyst such as 10% palladium on charcoal affords compounds of formula (15):



(15)

Alkylation or acylation of the ester enolate derived from formula (15) affords compounds wherein P_1 and P_2 are as defined in formula (1).

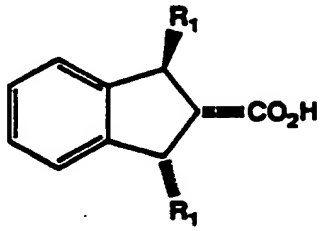
Alternatively, hydrogenation of compounds of formula (13) with hydrogen gas under pressure at approximately 60 psi in the presence of a suitable catalyst such as 10% palladium on charcoal in a suitable solvent such as ethyl acetate or methanol containing 1-5% acetic acid affords compounds of formula (15). Treatment of these compounds with a base such as sodium hydroxide in a suitable solvent such as aqueous ethanol provides racemic compounds of formula (16):



(16)

wherein Z_1, Z_2 and Z_3 are hydrogen; $R_1 = R_2$; and n is 0. Treatment of compounds of formula (13) with triethylsilane and boron trifluoride etherate in a suitable solvent such as dichloromethane at 0°C followed by r action with samarium II iodide in a suitable

solvent such as tetrahydrofuran and then saponification, provides compounds of formula (17)



(17)

With appropriate manipulation and protection of any chemical functionalities, synthesis of the remaining compounds of the Formula (I) is accomplished by methods analogous to those above and to those described in the Experimental section.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium

stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucros . Where th composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a

single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

I. <u>Binding Assay</u>

A) <u>Membrane Preparation</u>

Rat cerebellum or kidney cortex were rapidly dissected and frozen immediately in liquid nitrogen or used fresh. The tissues, 1-2 g for cerebellum or 3-5 g for kidney cortex, were homogenized in 15 mls of buffer containing 20mM Tris HCl and 5mM EDTA, pH 7.5 at 4°C

using a motor-driven homogenizer. The homogenates were filtered through cheesecloth and centrifuged at 20,000 x g for 10 minutes at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 minutes at 4°C. The resulting pellet was resuspended in a small volume of buffer containing 50 mM Tris, 10 mM $MgCl_2$, pH 7.5; aliquotted with small vials and frozen in liquid nitrogen. The membranes were diluted to give 1 and 5 mg of protein for each tube for cerebellum and kidney cortex in the binding assay.

Freshly isolated rat mesenteric artery and collateral vascular bed were washed in ice cold saline (on ice) and lymph nodes were removed from along the major vessel. Then, the tissue was homogenized using a polytron in buffer containing 20 mM Tris and 5mM EDTA, pH 7.5 at 4°C in 15 ml volume for ~6 gm of mesenteric artery bed. The homogenate was strained through cheesecloth and centrifuged at 2,000 xg for 10 min. at 4°C. The supernatant was removed and centrifuged at 40,000 xg for 30 min. at 4°C. The resulting pellet was resuspended as explained above for cerebellum and kidney cortex. Approximately 10 mg of membrane protein was used for each tube in binding experiments.

B) [^{125}I]ET-1 Binding Protocol

[^{125}I]ET-1 binding to membranes from rat cerebellum (2-5 mg protein/assay tube) or kidney cortex (3-8 mg protein/assay tube) were measured after 60 minutes incubation at 30°C in 50 mM Tris HCl, 10 mM $MgCl_2$, 0.05% BSA, pH 7.5 buffer in a total volume of 100 ml. Membrane protein was added to tubes containing either buffer or indicated concentration of compounds. [^{125}I]ET-1 (2200 Ci/mmol) was diluted in the same buffer containing BSA to give a final concentration of 0.2-0.5 nM ET-1. Total and nonspecific binding were measured in the absence and presence of 100 nM unlabelled ET-1. After the incubation, the reactions were stopped with

3.0 ml cold buffer containing 50 mM Tris and 10 mM $MgCl_2$, pH 7.5. Membrane bound radioactivity was separated from free ligand by filtering through Whatman GF/C filter paper and washing the filters 5 times with 3 ml of cold buffer using a Brandel cell harvester. Filter papers were counted in a gamma counter with an efficiency of 75%. IC_{50}'s for the compounds of this invention range from 0.1 nm to 50 μm.

II. In Vitro Vascular Smooth Muscle Activity

Rat aorta are cleaned of connective tissue and adherent fat, and cut into ring segments approximately 3 to 4 mm in length. Vascular rings are suspended in organ bath chambers (10 ml) containing Krebs-bicarbonate solution of the following composition (millimolar): NaCl, 112.0; KCl, 4.7; KH_2PO_4, 1.2; $MgSO_4$, 1.2; $CaCl_2$, 2.5; $NaHCO_3$, 25.0; and dextrose, 11.0. Tissue bath solutions are maintained at 37°C and aerated continuously with 95% O_2/ 5% CO_2. Resting tensions of aorta are maintained at 1 g and allowed to equilibrate for 2 hrs., during which time the bathing solution is changed every 15 to 20 min. Isometric tensions are recorded on Beckman R-611 dynographs with Grass FT03 force-displacement transducer. Cumulative concentration-response curves to ET-1 or other contractile agonists are constructed by the method of step-wise addition of the agonist. ET-1 concentrations are increased only after the previous concentration produces a steady-state contractile response. Only one concentration-response curve to ET-1 is generated in each tissue. ET receptor antagonists are added to paired tissues 30 min prior to the initiation of the concentration-response to contractile agonists.

ET-1 induced vascular contractions are expressed as a percentage of the response elicited by 60 mM KCl for each individual tissue which is determined at

the beginning of each experiment. Data are xpressed as the mean ± S.E.M. Dissociation constants (K_b) of competitive antagonists were determined by the standard method of Arunlakshana and Schild. The potency range for compounds of this invention range from 0.1 nM to 50 µm.

The following examples are illustrative and are not limiting of the compounds of this invention.

EXAMPLE 1

(1RS,2RS,3SR)-1-(4-Methoxyphenyl)-3-phenylindane-2-carboxylic acid

a) Ethyl (1RS)[1-Hydroxy-1-(4-methoxyphenyl)]-3-phenylindene-2-carboxylate. To dry magnesium turnings (0.88 g, 36 mmol) under an argon atmosphere was added, portionwise, a solution of p-bromoanisole (4.5 ml, 36 mmol) in 5% THF/ Et_2O (37 ml). The resulting p-methoxyphenyl magnesium bromide solution was added to a solution of ethyl 1-oxo-3-phenylindene-2-carboxylate (5.0 g, 18 mmol) in Et_2O (300 ml) under an argon atmosphere at 0°C. The resulting mixture was allowed to warm to room temperature and was stirred for 10 min. The mixture was partitioned between 3M HCl (100 ml) and EtOAc (200 ml). The organic extract was washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried (Na_2SO_4). The solvent was removed *in vacuo* to provide a yellow oil which was treated with Et_2O/ hexanes. The solid which formed was collected by filtration (3.47 g). The filtrate was concentrated under reduced pressure and purified by flash chromatography. The material which was isolated was treated with Et_2O/ hexanes, and the additional solid which formed (1.76 g, 75% total yield) was collected by filtration to afford the title compound.

b) Ethyl (RS)-1-(4-Methoxyphenyl)-3-phenylindene-2-carboxylate. To a solution of ethyl (1RS) [1-hydroxy-1-(4-methoxyphenyl)]-3-phenylindene-2-carboxylate (4.65 g, 12.0 mmol) in CH_2Cl_2 (40 ml) at 0°C under an argon atmosphere was added triethylsilane (2.34 ml, 14.6 mmol), followed by boron trifluoride etherate (8.8 ml, 71 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 10 min, at which time was added slowly 3M HCl (50 ml). The mixture was extracted with EtOAc (150 ml). The organic extract was washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel, eluting with 10% EtOAc/ hexanes to provide the title compound (4.2 g, 95%) as a mixture of Δ1 and Δ2 double bond isomers.

c) Ethyl (1RS,2SR,3SR)-1-(4-Methoxyphenyl)-3-phenylindane-2-carboxylate. To a solution of ethyl (RS)-1-(4-methoxyphenyl)-3-phenylindene-2-carboxylate (5.75 g, 15 mmol) in EtOAc (150 ml) was added 5% palladium on activated carbon (600 mg). The resulting suspension was stirred under an atmosphere of H_2 for 1 d, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the title compound, which was used without further purification.

d) (1RS,2RS,3SR)-1-(4-Methoxyphenyl)-3-phenylindane-2-carboxylic acid. To a solution of ethyl (1RS,2SR,3SR)-1-(4-methoxyphenyl)-3-phenylindane-2-carboxylate, (5.5 g, 14.8 mmol) in EtOH (70 ml) was added 5M NaOH (9 ml, 45 mmol). The resulting mixture was stirred under an argon atmosphere for 1 d, at which time H_2O (70 ml) was added. The mixture was concentrated under reduced pressure. The aqueous residue was xtracted with Et_2O,

and the Et_2O extracts were discarded. The aqueous phase was acidified with 6M HCl and extracted several times with EtOAc. The combined EtOAc xtracts were washed successively with H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to provide an oily residue which crystallized upon standing. The solid material was recrystallized from EtOAc/ hexanes to afford the title compound (4.25 g, 83%); m.p. 164 - 166°C.

^{1}H NMR ($CDCl_3$) : δ 7.35 - 7.18 (m, 9H); 6.92 - 6.88 (m, 4H); 4.68 (d, 1H, J = 10 Hz); 4.64 (d, 1H, J = 10 Hz); 3.81 (s, 3H); 3.34 (t, 1H, J = 10 Hz).

MS : 345 [$(M+H)^+$].

Anal. Calc. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85.

Found C, 80.21; H 6.03.

EXAMPLE 2

(trans, trans)-1,3-Di(4-methoxyphenyl)-indane-2-carboxylic acid

a) Ethyl 2-Benzoyl-3-(4-hydroxyphenyl)propenoate. To a solution of 4-hydroxybenzaldehyde (31.7 g, 0.26 mol) and ethyl benzoylacetate (45.5 ml, 0.26 mol) in EtOH (45 ml) under an argon atmosphere was added piperidine (2.6 ml, 0.026 mol) and acetic acid (3 drops). After stirring at room temperature overnight, the resulting solid mixture was treated with hot EtOH (700 ml), and then allowed to cool. The crystals which formed were collected by filtration to afford the title compound (61.0 g, 79%).

b) Ethyl (2RS,3SR)-3-(4-Hydroxyphenyl)-1-oxoindane-2-carboxylate. To a mixture of ethyl 2-benzoyl-3-(4-hydroxyphenyl)propenoate (0.50 g, 1.7 mmol) in CH_2Cl_2 (15 ml) at 0°C under an argon atmosphere was added titanium tetrachloride (0.93 ml, 8.3 mmol). The resulting mixture was allowed to stir at room temp rature ov rnight. The reaction was slowly quenched

with 3M HCl, then partitioned betw en EtOAc (50 ml) and 3M HCl. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with H_2O and saturated aqueous NaCl, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the solid residue was recrystallized from EtOAc/ hexanes to afford the title compound (410 mg, 82%).

c) Ethyl (2RS,3SR)-3-(4-t-Butyldimethylsiloxyphenyl)-1-oxoindane-2-carboxylate. To a solution of ethyl (2RS,3SR)-3-(4-hydroxyphenyl)-1-oxoindane-2-carboxylate (3.0 g, 10.2 mmol) in DMF (10 ml) under an argon atmosphere were added imidazole (1.72 g, 25.3 mmol) and t-butyldimethylchloro-silane (1.82 g, 12.1 mmol). The resulting mixture was allowed to stir at room temperature for 3 d, then was poured into dilute aqueous HCl and extracted with EtOAc (2x). The combined organic extracts were washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to provide the title compound (5.40 g) which was used without further purification.

d) Ethyl 3-(4-t-Butyldimethylsiloxyphenyl)-1-oxoindene-2-carboxylate. To a solution of ethyl (2RS,3SR)-3-(4-t-butyldimethylsiloxyphenyl)-1-oxoindane-2-carboxylate (130 mg, 0.32 mmol) in CH_2Cl_2 (3 ml) under an argon atmosphere was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (80 mg, 0.35 mmol). The resulting mixture was stirred for 2.5 h. Aqueous $NaHSO_3$ and EtOAc were added, and the mixture was stirred for 5 min. The aqueous phase was separated and extracted with EtOAc, and the combined organic extracts were washed successively with aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo*, and the residue was purified by flash

chromatography on silica g l to afford the title compound (110 mg, 85%).

e) Ethyl (1RS)-3-(4-t-Butyldimethylsiloxyphenyl)-1-hydroxy-1-(4-methoxyphenyl)indene-2-carboxylate. To dry magnesium turnings (119 mg, 4.9 mmol) under an argon atmosphere was added, portionwise, a solution of p-bromoanisole (0.61 ml, 4.9 mmol) in 9 : 1 Et_2O/ THF (10 ml). The resulting p-methoxyphenyl magnesium bromide solution was added to a solution of ethyl 3-(4-t-butyldimethylsiloxyphenyl)-1-oxoindene-2-carboxylate (1.00 g, 2.5 mmol) in Et_2O (60 ml) under an argon atmosphere at 0°C. The resulting mixture was allowed to warm to room temperature and was stirred for 5 min. The mixture was partitioned between 3M HCl and EtOAc. The organic extract was washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to provide the title compound (1.47 g) which was used without further purification.

f) Ethyl (RS)-1-(4-t-Butyldimethylsiloxyphenyl)-3-(4-methoxyphenyl)indene-2-carboxylate. To a solution of ethyl (1RS)-3-(4-t-butyldimethylsiloxyphenyl)-1-hydroxy-1-(4-methoxyphenyl)indene-2-carboxylate (2.5 mmol, prepared above) in CH_2Cl_2 (10 ml) at 0°C under an argon atmosphere was added triethylsilane (0.48 ml, 3.0 mmol), followed by boron trifluoride etherate (1.8 ml, 14.6 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 10 min, at which time was added slowly 3M HCl. The mixture was extracted with EtOAc. The organic extract was washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography on silica gel, luting with 15% Et_2O/ h xanes to provide the title

compound as a mixture of Δ1 and Δ2 double bond isomers (820 mg, 67% for two steps).

g) Ethyl (1RS,2SR,3SR)-1-(4-t-Butyldimethylsiloxyphenyl)-3-(4-methoxyphenyl)indane-2-carboxylate. To a solution of ethyl (RS)-3-(4-t-butyldimethylsiloxyphenyl)-1-(4-methoxyphenyl)indene-2-carboxylate (mixture of Δ1 and Δ2 double bond isomers) (750 mg, 1.5 mmol) in EtOH (25 ml) was added 5% palladium on activated carbon (70 mg). The resulting suspension was stirred under an atmosphere of H_2 for 18 h, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the title compound (730 mg, 97%), which was used without further purification.

h) Ethyl (1RS,2RS,3SR)-1-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)indane-2-carboxylate. To a solution of ethyl (1RS,2SR,3SR)-1-(4-t-butyldimethylsiloxyphenyl)-3-(4-methoxyphenyl)indane-2-carboxylate (723 mg, 1.4 mmol) in EtOH (20 ml) was added 1M NaOH (1.6 ml, 1.6 mmol), and the resulting mixture was stirred at room temperature for 30 min. The mixture was then partitioned between 3M HCl and EtOAc. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to afford the title compound (554 mg, 100%).

i) Ethyl (cis, cis)-1,3-Di(4-methoxyphenyl)indane-2-carboxylate. To a solution of ethyl (1RS,2RS,3SR)-1-(4-hydroxyphenyl)-3-(4-methoxyphenyl)indane-2-carboxylate (270 mg, 0.7 mmol) in acetonitrile (5 ml) at 0°C was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.25 ml, 1.7 mmol), followed by methyl iodide (0.5 ml, 8.0 mmol). The resulting mixture was allowed to warm to room temperature and was stirred overnight. The mixture was

partitioned between EtOAc and dilute aqueous HCl. The organic extract was washed with saturated aqueous NaCl and dried. Th solvent was removed *in vacuo*, and th residue was purified by flash chromatography to afford the title compound (40 mg, 32% based on recovered starting material).

j) (trans, trans)-1,3-Di(4-methoxyphenyl)indane-2-carboxylic acid. To a solution of ethyl (cis, cis)-1,3-di(4-methoxyphenyl)indane-2-carboxylate (35 mg, 0.09 mmol) in EtOH (3 ml) was added 1M NaOH (0.25 ml, 0.25 mmol), and the resulting mixture was allowed to stir at room temperature overnight. Thin layer chromatographic analysis at this time indicated that the reaction was incomplete, so 5M NaOH (0.15 ml, 0.75 mmol) was added, and the mixture was allowed to stand at 0°C for 5 days. Water was added, and the mixture was concentrated under reduced pressure. The aqueous residue was extracted with Et_2O (2x), and the Et_2O extracts were discarded. The aqueous phase was acidified with 6M HCl and extracted several times with EtOAc. The combined EtOAc extracts were washed successively with H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to provide an oily residue which crystallized upon standing. The solid material was recrystallized from EtOAc/ hexanes to afford the title compound (19 mg, 59%); m.p. 192 - 193°C.

^{1}H NMR (acetone-d_6) : δ 7.25 (dd, 4H, J = 6.6 Hz, 2.1 Hz); 7.21 - 7.18 (m, 2H); 6.92 (dd, 4H, J = 6.6 Hz, 2.1 Hz); 6.86 - 6.83 (m, 2H); 4.59 (d, 2H, J = 10 Hz); 3.79 (s, 6H); 3.26 (t, 1H, J = 10 Hz). MS : 392 [$(M+NH_4)^+$].

Anal. Calc. for $C_{24}H_{22}O_4$: C, 76.99; H, 5.92.
Found C, 76.74; H 6.15.

EXAMPLE 3

(1RS,2SR,3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid

a) 2-(3,4-Methylenedioxybenzoyl)benzoic acid. To a solution of 2-bromobenzoic acid (12 g, 0.06 mol) in THF (200 ml) at -100°C under an argon atmosphere was added dropwise *n*-butyl lithium (50 ml of 2.5M solution in hexanes, 0.125 mol), maintaining the temperature below -90°C. Upon completion of the addition, the resulting solution was stirred at -100°C for 1 h, at which time was added slowly a solution of piperonylic acid chloride (11 g, 0.06 mol) in THF (50 ml), maintaining the temperature below -90°C. The resulting mixture was allowed to warm to -80°C and stirred for 1 h, then was allowed to slowly warm to room temperature and left to stand for 48 h. The reaction mixture was concentrated under reduced pressure, and the residue was partitioned between Et_2O and 1M HCl. The organic phase was extracted with 10% aqueous NaOH. The NaOH extract was acidified with concentrated HCl, and the combined aqueous material was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with a solvent gradient of 10 → 30% EtOAc/ 0.1% HOAc/hexanes to afford the title compound as an off-white solid (4.5 g, 28%).

b) Diethyl 2-[2-(3,4-Methylenedioxybenzoyl)benzoyl-malonate. A solution of 2-(3,4-methylenedioxybenzoyl)-benzoic acid (4.0 g, 14.8 mmol) in thionyl chloride (30 ml) was heated at reflux for 2 h, then allowed to cool and was concentrated under reduced pressure. The residue was dissolved in Et_2O (50 ml) and to this was added a solution of diethyl magnesium malonate [prepared by the method of Walker and Hauser, JACS, *68*, 1386

(1946) using magnesium (0.8 g, 33.3 mmol) and diethyl malonate (4.9 g, 30.6 mmol)] in Et_2O. Th resulting mixture was heated at reflux for 1 h, then allowed to cool and was poured into ice-cold 10% aqueous H_2SO_4 (100 ml). The aqueous phase was extracted with Et_2O, and the combined organic material was washed with saturated aqueous NaCl and dried. The solvent was removed under reduced pressure to afford the title compound as an orange oil, which was used without further purification.

c) Ethyl 3-(3,4-Methylenedioxyphenyl)-1-oxoindene-2-carboxylate. A solution containing diethyl 2-[2-(3,4-methylenedioxybenzoyl)benzoylmalonate (crude material prepared above) in 5% aqueous Na_2CO_3 (100 ml) was heated at reflux for 10 min. The reaction mixture was then allowed to cool, and the aqueous material was removed by decantation. The residue was placed in H_2O (50 ml), and the mixture was heated at reflux, cooled and concentrated under reduced pressure. The residue was recrystallized from hexanes to afford the title compound as a yellow solid (5.0 g, 100% for two steps).

d) Ethyl (1RS)-1-Hydroxy-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. A solution of 4-bromoanisole (0.89 g, 5.0 mmol) in 9 : 1 Et_2O/ THF (10 ml) was added to magnesium turnings (0.105 g, 5.0 mmol), and the resulting mixture was allowed to stir for 30 min. The resultant 4-methoxyphenyl magnesium bromide was added dropwise to a solution of ethyl 3-(3,4-methylenedioxyphenyl)-1-oxoindene-2-carboxylate (0.77 g, 2.4 mmol) in 10 : 1 Et_2O/ THF (55 ml) at 0°C. The resulting mixture was stirred at 0°C for 1 h and was then partitioned between EtOAc and 1M HCl. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). The

solvent was removed under reduc d pressure, and the residue was purified by flash chromatography on silica gel, eluting with 10% EtOAc/ hexanes to afford the title compound as a yellow glassy solid (0.80 g, 80%).

e) Ethyl (RS)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl (1RS)-1-hydroxy-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-indene-2-carboxylate (0.80 g, 1.9 mmol) in CH_2Cl_2 (10 ml) at 0°C under an argon atmosphere was added triethylsilane (0.28 g, 2.4 mmol), followed by boron trifluoride etherate (1 ml, 8.1 mmol). The resulting solution was stirred at 0°C for 10 min, and was then partitioned between EtOAc and 3M HCl. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was filtered through a pad of silica gel, eluting with CH_2Cl_2. The title compound (mixture of Δ1 and Δ2 double bond isomers) was obtained as a glassy, yellow solid (0.72 g, 94%).

f) Ethyl(1RS,2RS,3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate. To a solution of ethyl (RS)-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-indene-2-carboxylate (0.72 g, 1.7 mmol) in EtOH (30 ml) was added 10% palladium on activated carbon (1 g). The resulting suspension was stirred under an atmosphere of H_2 for 56 h and filtered. The filtrate was concentrated under reduced pressure to afford the title compound as a yellow solid (0.70 g, 95%), which was used without further purification.

g) (1RS,2SR,3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid. To a solution of ethyl (1RS,2RS,3SR)-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate (0.10 g,

0.2 mmol) in EtOH (5 ml) was added a solution of sodium hydroxid (0.10 g, 2.5 mmol) in H_2O (2 ml). The resulting mixture was stirred at room temperature overnight. The mixture was acidified, and the solid which formed was collected by filtration and dried under reduced pressure to afford the title compound as a tan solid (0.04 g, 86%).

^{1}H NMR ($CDCl_3$) : δ 7.25 (m, 5H); 6.90 (m, 4H); 6.77 (d, 2H, J = 7 Hz); 5.95 (m, 2H); 4.61 (d, 2H, J = 10 Hz); 3.81 (s, 3H); 3.25 (t, 2H, J = 10 Hz). MS : 387 [(M-H$^+$].

Anal. Calc. for $C_{24}H_{20}O_5 \cdot {}^1/_8\ H_2O$: C, 73.79; H, 5.22. Found C, 76.73; H 5.21.

EXAMPLE 4

(1RS, 2SR, 3SR)-1-(4-Fluorophenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid

a) Ethyl (1RS)-1-(4-Fluorophenyl)-1-hydroxy-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl 3-(3,4-methylenedioxyphenyl)-1-oxoindene-2-carboxylate (100 mg, 0.31 mmol) in THF (5 ml) under an argon atmosphere at 0°C was added a solution of freshly prepared 4-fluorophenyl magnesium bromide (0.62 mmol). After stirring for 45 min, the mixture was partitioned between 3M HCl and EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$ and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 15% EtOAc/ hexanes to afford the title compound (45 mg, 35%).

b) Ethyl (RS)-1-(4-Fluorophenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl (1RS)-1-(4-fluorophenyl)-1-hydroxy-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate (45 mg, 0.11 mmol) in CH_2Cl_2 (3 ml) at 0°C was added triethylsilane

(38 µl, 0.24 mmol), followed by boron trifluoride etherate (121 µl, 0.98 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 15 min, at which time was added slowly 3M HCl. The mixture was extracted with EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$ and saturated aqueous NaCl. The solvent was removed *in vacuo* to provide the title compound (40 mg, 90%) as a mixture of Δ1 and Δ2 double bond isomers.

c) Ethyl (1RS, 2RS, 3SR)-1-(4-Fluorophenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate. To a solution of ethyl (RS)-1-(4-fluorophenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate (40 mg, 0.10 mmol) in EtOH (3 ml) was added 10% palladium on activated carbon (45 mg). The resulting suspension was stirred under an atmosphere of H_2 overnight, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the title compound (40 mg, 100%), which was used without further purification.

d) (1RS, 2SR, 3SR)-1-(4-Fluorophenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid. To a solution of ethyl (1RS, 2RS, 3SR)-1-(4-fluorophenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate (60 mg, 0.15 mmol) in EtOH (0.5 ml) was added 6M KOH (0.14 ml, 0.84 mmol). The resulting mixture was allowed to stir at room temperature overnight, then was concentrated under reduced pressure. The residue was partitioned between H_2O and Et_2O. The aqueous phase was acidified with 3M HCl and extracted several times with EtOAc. The combined EtOAc extracts were washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford an oil, which was crystallized from EtOAc/ hexan s. The title compound

was obtained as an off-white crystalline solid (22 mg, 39%); m.p. 146 - 149°C.

^{1}H NMR ($CDCl_3$) : δ 7.23 (m, 4H); 6.96 (m, 1H); 6.90 (m, 1H); 6.79 (s, 2H); 6.75 (s, 1H); 5.96 (m, 2H); 4.62 (apparent br t, 2H, J = 10 Hz); 3.25 (t, 1H, J = 10 Hz).

MS m/e (rel. int.) : 753 [$(2M+1)^+$, 3].

Anal. Calcd. for $C_{23}H_{17}FO_4$: C, 73.40; H, 4.55.

Found: C, 73.19; H, 4.45.

EXAMPLE 5

(1RS, 2SR, 3SR)-1-(3-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid

a) Ethyl (1RS)-1-Hydroxy-1-(3-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl 3-(3,4-methylenedioxyphenyl)-1-oxoindene-2-carboxylate (100 mg, 0.31 mmol) in THF (2 ml) under an argon atmosphere at 0°C was added a solution of freshly prepared 3-methoxyphenyl magnesium bromide (0.31 mmol). After stirring for 15 min, additional 3-methoxyphenyl magnesium bromide (0.06 mmol) was added. Stirring was continued for 45 min, at which time thin layer chromatographic analysis indicated that the reaction was incomplete. Additional 3-methoxyphenyl magnesium bromide (0.12 mmol) was added. After stirring for 2 h more, the mixture was partitioned between 3M HCl and EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl. The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 15% EtOAc/ hexanes to afford the title compound (150 mg, 100%).

b) Ethyl (1RS)-1-(3-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl (1RS)-1-hydroxy-1-(3-methoxyphenyl)-3-(3,4-

methylenedioxyphenyl)-indene-2-carboxylate (150 mg, 0.35 mmol) in CH_2Cl_2 was added tri thylsilane (67 µl, 0.42 mmol), followed by boron trifluoride etherate (213 µl, 1.73 mmol). The reaction mixtur was allowed to stir for 30 min, at which time was added slowly 5% aqueous HCl. The mixture was extracted with EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to provide the title compound (45 mg, 31%) as a mixture of Δ1 and Δ2 double bond isomers.

c) Ethyl (RS, 2RS, 3SR)-1-(3-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate. To a solution of ethyl (RS)-1-(3-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indene-2-carboxylate (45 mg, 0.11 mmol) in EtOH (3 ml) was added 10% palladium on activated carbon (45 mg). The resulting suspension was shaken on a Parr hydrogenator at 50 psi H_2 overnight, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the title compound (43 mg, 94%), which was used without further purification.

d) (1RS, 2SR, 3SR)-1-(3-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid. To a solution of ethyl (1RS, 2RS, 3SR)-1-(3-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylate (43 mg, 0.10 mmol) in EtOH (1 ml) was added 6M KOH (0.10 mL, 0.60 mmol). The resulting mixture was allowed to stir at room temperature overnight, then was partitioned between H_2O and Et_2O. The aqueous phase was acidified with 3M HCl and extracted several times with EtOAc. The combined EtOAc extracts were washed successively with

H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford an oil, which was crystallized from Et_2O/ hexanes. The title compound was obtained as a solid; m.p. 131 - 133°C.

^1H NMR ($CDCl_3$) : δ 7.21 (m, 3H); 6.97 - 6.73 (m, 8H); 5.95 (m, 2H); 4.61 (apparent br t, 2H, J = 9 Hz); 3.67 (s, 3H); 3.30 (t, 1H, J = 9 Hz).

MS m/e (rel. int.) : 777 [$(2M+1)^+$, 65].

Anal. Calcd. for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19.

Found: C, 74.71; H, 5.47.

EXAMPLE 6

(1RS, 3RS)-1,3-Di-(3,4-methylenedioxyphenyl)-indane-2-carboxylic acid

a) Ethyl (1RS)-1,3-di-(3,4-methylenedioxyphenyl)-1-hydroxyindene-2-carboxylate. To dry magnesium turnings (0.25 g, 10 mmol) under an argon atmosphere was added a solution of 4-bromo-1,2-methylenedioxybenzene (2.1 g, 10 mmol) in 1 : 10 THF/ Et_2O (22 ml). The resulting solution was allowed to stir at room temperature for 2 h. During this time, additional THF (4 ml) was added. The resulting 3,4-methylenedioxyphenylmagnesium bromide was added to a solution of ethyl 3-(3,4-methylenedioxyphenyl)-1-oxoindene-2-carboxylate (0.50 g, 2 mmol) in 1 : 4 THF/ Et_2O (25 ml) under an argon atmosphere at 0°C. The resulting mixture was stirred at 0°C for 15 min, at which time 1M HCl (50 ml) was added. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to afford the title compound as a yellow solid (0.29 g, 42%).

b) Ethyl (RS)-1,3-Di-(3,4-methylenedioxyphenyl)indene-2-carboxylate. To a solution of ethyl (1RS)-1,3-di-(3,4-methylenedioxyphenyl)-1-hydroxyinden -2-carboxylate (0.29 g, 0.65 mmol) in CH_2Cl_2 (3 ml) at 0°C under an argon atmosphere was added triethylsilane (91 mg, 0.78 mmol), followed by boron trifluoride etherate (0.3 ml, 2.4 mmol). The reaction mixture was stirred for 10 min, at which time was added ice-cold 1M HCl, and the mixture was extracted with EtOAc. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was placed on a small pad of silica gel, eluting with CH_2Cl_2 to provide the title compound (257 mg, 92%).

c) Ethyl (1RS, 3RS)-1,3-Di-(3,4-methylenedioxyphenyl)indane-2-carboxylate. Ethyl (RS)-1,3-di-(3,4-Methylenedioxyphenyl)indene-2-carboxylate (163 mg, 0.38 mmol) was placed in MeOH (0.05 ml), and to this was added SmI_2 (10 ml of 0.1M solution in THF, 1.0 mmol). The resulting mixture was stirred under an argon atmosphere overnight, at which time thin layer chromatographic analysis indicated that the reaction was incomplete. Additional SmI_2 (5ml of 0.1M solution in THF, 0.5 mmol) was added, and stirring was continued for 2 h. The reaction mixture was partitioned between Et_2O and 5% aqueous $Na_2S_2O_3$. The organic extract was washed with saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to afford the title compound as a colorless, glassy solid (120 mg, 75%).

d) (1RS, 3RS)-1,3-Di-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid. To a solution of ethyl (1RS, 3RS)-1,3-di-(3,4-methylenedioxyphenyl)indane-2-carboxylate

(75 mg, 0.17 mmol) in EtOH (20 ml) was added NaOH (0.10 g, 2.5 mmol). The resulting mixture was allowed to stir at room temperatur for 3 d, at which tim thin lay r chromatographic analysis indicated that the reaction was incomplete. The mixture was then heated at reflux for 36 h, allowed to cool and was concentrated under reduced pressure. To the residue was added concentrated HCl, and the solid which formed was collected by filtration and dried. The solid was triturated with boiling hexanes to afford the title compound as a white solid (50 mg, 73%); m.p. 182 - 185°C.

^{1}H NMR ($CDCl_3$) : δ 7.25 (m, 2H); 7.15 (m, 1H); 7.00 (m, 1H); 6.76 (s, 2H); 6.68 (m, 2H); 6.50 (dd, 1H, J = 8, 1 Hz); 6.40 (d, 1H, J = 2 Hz); 5.94 (s, 2H); 5.90 (d, 1H, J = 1 Hz); 5.87 (d, 1H, J = 1 Hz); 4.84 (d, 1H, J = 10 Hz); 4.78 (d, 1H, J = 10 Hz); 3.63 (dd, 1H, J = 10 Hz, 9 Hz).

MS : 402 $(M)^+$.

Anal. Calcd. for $C_{24}H_{18}O_6 \cdot 1/5\ H_2O$: C, 71.00; H, 4.52. Found: C, 71.13; H, 4.46.

EXAMPLE 7

(trans, trans)-1,3-Di-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid

a) Ethyl (cis, cis)-1,3-Di-(3,4-methylenedioxyphenyl)-indane-2-carboxylate. To a solution of ethyl (RS)-1,3-di-(3,4-methylenedioxyphenyl)indene-2-carboxylate (93 mg, 0.22 mmol) in EtOH (2 ml) was added 10% palladium on activated carbon (0.10 g). The resulting suspension was shaken on a Parr hydrogenator at 55 psi H_2 for 2 d, then was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure to afford the title compound (45 mg, 48%) as a glassy, yellow solid, which was used without further purification.

b) (trans, trans)-1,3-Di-(3,4-methylenedioxyphenyl)-indane-2-carboxylic acid. To a solution of ethyl (cis, cis)-1,3-di-(3,4-methylenedioxyphenyl)indane-2-carboxylate (45 mg, 0.1 mmol) in 2 : 1 EtOH/ H_2O (15 ml) was added sodium hydroxide (50 mg, 1.2 mmol). The resulting solution was allowed to stir at room temperature overnight, then was concentrated under reduced pressure. The residue was treated with concentrated HCl, and the solid which formed was collected by filtration and dried. The solid was recrystallized from Et_2O/ hexanes to afford the title compound as a light tan solid (12 mg, 30%); m.p. 188 - 191°C.

EXAMPLE 8

(1RS, 2RS, 3SR)-1-(3,4-Methylenedioxyphenyl)-3-phenylindane-2-carboxylic acid

a) Ethyl (1RS)-1-Hydroxy-1-(3,4-methylenedioxyphenyl)-3-phenylindene-2-carboxylate. To a solution of ethyl 1-oxo-3-phenylindene-2-carboxylate (1.0 g, 3.6 mmol) in THF (35 ml) under an argon atmosphere at 0°C was added a solution of freshly prepared 3,4-methylenedioxyphenyl magnesium bromide (5.4 mmol). After stirring for 30 min, the mixture was partitioned between 3M HCl and EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$ and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo*, and the residue was purified by flash chromatography, eluting with 10% EtOAc/ hexanes to afford the title compound (1.03 g, 72%).

b) Ethyl (RS)-1-(3,4-Methylenedioxyphenyl)-3-phenyl-indene-2-carboxylate. To a solution of ethyl (1RS)-1-hydroxy-1-(3,4-methylenedioxyphenyl)-3-phenylindene-2-carboxylate (1.03 g, 2.58 mmol) in CH_2Cl_2 (40 mL) was added triethylsilane (0.49 ml, 3.07 mmol), followed by

boron trifluoride etherate (1.55 ml, 12.6 mmol). The reaction mixture was allow d to stir for 15 min, at which time was added slowly 3M HCl. The mixture was extracted with EtOAc. The organic extract was washed successively with H_2O, 5% aqueous $NaHCO_3$ and saturated aqueous NaCl. The solvent was removed *in vacuo* to provide the title compound (1.00 g, 100%) as a mixture of Δ1 and Δ2 double bond isomers.

c) Ethyl (1RS, 2SR, 3SR)-1-(3,4-Methylenedioxyphenyl)-3-phenylindane-2-carboxylate. To a solution of ethyl (RS)-1-(3,4-methylenedioxyphenyl)-3-phenylindene-2-carboxylate (1.00 g, 2.60 mmol) in EtOH (25 ml) was added 10% palladium on activated carbon (30 mg). The resulting suspension was stirred under an atmosphere of H_2 overnight. Thin layer chromatographic analysis indicated that the reaction was incomplete, so additional 10% palladium on activated carbon (30 mg) was added, and the mixture was shaken on a Parr hydrogenator at 30 psi H_2 for 2 d. At this time, thin layer chromatographic analysis again indicated that the reaction was incomplete. The reaction mixture was filtered through a pad of Celite, and 10% palladium on activated carbon (250 mg) was added. The reaction mixture was shaken on a Parr hydrogenator at 60 psi H_2 overnight. Filtration and repetition of the latter hydrogenation conditions led to complete consumption of starting material. The reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure to afford the title compound (650 mg, 65%), which was used without further purification.

d) (1RS, 2RS, 3SR)-1-(3,4-Methylenedioxyphenyl)-3-phenylindane-2-carboxylic acid. To a solution of ethyl (1RS, 2SR, 3SR)-1-(3,4-methylenedioxyphenyl)-3-

phenylindane-2-carboxylate (650 mg, 1.68 mmol) in EtOH containing a few drops of THF was added 6M KOH (1.68 ml, 10.1 mmol). The resulting mixture was allowed to stir at room temperature overnight, then was concentrated under reduced pressure. The residue was partitioned between H_2O and Et_2O. The aqueous phase was acidified with 3M HCl and extracted several times with EtOAc. The combined EtOAc extracts were washed successively with H_2O and saturated aqueous NaCl and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford an oil, which was crystallized from EtOAc/ hexanes. The title compound was obtained as a solid (305 mg, 51%); m.p. 186 - 187°C. Anal. Calcd. for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 76.60; H, 5.08.

EXAMPLE 9

(1RS, 2SR, 3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-2-(tetrazol-5-yl)indane

a) (1RS, 2SR, 3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxamide. A mixture of (1RS, 2SR, 3SR)-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carboxylic acid (250 mg, 0.64 mmol) in $SOCl_2$ (2.5 ml) was allowed to stir overnight under an argon atmosphere. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in benzene (5 ml). To the resulting mixture under an argon atmosphere was added concentrated NH_4OH (5 ml). The solid which formed was collected by filtration, washed with H_2O and dried *in vacuo* to afford the title compound (185 mg, 75%).

b) (1RS, 2SR, 3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)indane-2-carbonitrile. To ice-cold DMF (1 ml) under an argon atmosphere was added oxalyl chloride (68µl, 0.78mmol). After stirring for 5 min at 0°C, a solution of (1RS, 2SR, 3SR)-1-(4-methoxyphenyl)-

3-(3,4-methylenedioxyphenyl)indane-2-carboxamide (150 mg, 0.39 mmol) in DMF (2 ml) was added, and stirring was continu d for an additional 10 min at 0°C. The reaction mixture was partitioned between EtOAc and 3M HCl. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with H_2O, aqueous $NaHCO_3$, H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo* to afford the title compound as a white solid (135 mg, 94%) which was used without further purification.

c) (1RS, 2SR, 3SR)-1-(4-Methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-2-(tetrazol-5-yl)indane. To THF (2.5 ml) at -78°C under an argon atmosphere was added aluminum chloride (90 mg, 0.67 mmol). After slowly warming to room temperature, sodium azide (130 mg, 2.2 mmol) was added, and the resulting mixture was heated at 70°C for 5 min, then cooled to room temperature. To the reaction mixture was added a solution of (1RS, 2SR, 3SR)-1-(4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-indane-2-carbonitrile (125 mg, 0.34 mmol) in THF (2.5 ml). After heating at 70°C overnight, thin layer chromatographic analysis of the reaction mixture indicated the presence of starting material, so additional $Al(N_3)_3$ was prepared as above (1.34 mmol) in THF. To this was added the reaction mixture, and heating at 70°C was resumed for an additional 5 h. The mixture was partitioned between EtOAc and 3M HCl. The aqueous phase was extracted with EtOAc, and the combined organic extracts were washed successively with H_2O and saturated aqueous NaCl and dried. The solvent was removed *in vacuo*, and the residue was crystallized from EtOAc/ hexanes to afford the title compound (78 mg, 56%). A portion of this material was further purified by MPLC (LiChroprep RP-18, MeOH/H_2O=60/40) and then r crystallized; m.p. 155 - 157 C (EtOAc/ hexanes).